

DESCRIPTION**CLOSURE DEVICE**

5 This application is a continuation-in-part of U.S.
application Serial No. 10/335,075, filed December 31, 2002, which
is a continuation-in-part of U.S. patent application Serial No.
10/081,726, now Patent No. 6,623,510 and is a continuation-in-
part of U.S. patent application Serial No. 10/435,104, filed May
10 9, 2003, and is a continuation-in-part of U.S. patent application
Serial No. 09/732,178, filed December 7, 2000, the disclosures of
each of which are incorporated by reference herein.

FIELD OF THE INVENTION

15 The present invention relates generally to apparatus and
methods for engaging tissue and/or closing openings through
tissue, e.g., into body lumens, and more particularly to devices
for closing a puncture in a blood vessel or other body lumen
formed during a diagnostic or therapeutic procedure, and to
20 methods for making and using such devices.

BACKGROUND

Catheterization and interventional procedures, such as
angioplasty or stenting, generally are performed by inserting a
25 hollow needle through a patient's skin and intervening tissue

into the vascular system. A guide wire may then be passed through the needle lumen into the patient's blood vessel accessed by the needle. The needle may be removed, and an introducer sheath may be advanced over the guide wire into the vessel, e.g.,
5 in conjunction with or subsequent to a dilator. A catheter or other device may then be advanced through a lumen of the introducer sheath and over the guide wire into a position for performing a medical procedure. Thus, the introducer sheath may facilitate introduction of various devices into the vessel, while
10 minimizing trauma to the vessel wall and/or minimizing blood loss during a procedure.

Upon completion of the procedure, the devices and introducer sheath may be removed, leaving a puncture site in the vessel wall. External pressure may be applied to the puncture site
15 until clotting and wound sealing occur. This procedure, however, may be time consuming and expensive, requiring as much as an hour of a physician's or nurse's time. It is also uncomfortable for the patient, and requires that the patient remain immobilized in the operating room, catheter lab, or holding area. In addition,
20 a risk of hematoma exists from bleeding before hemostasis occurs.

Various apparatus have been suggested for percutaneously sealing a vascular puncture by occluding the puncture site. For example, U.S. Patent Nos. 5,192,302 and 5,222,974, issued to

Kensey et al., describe the use of a biodegradable plug that may be delivered through an introducer sheath into a puncture site. When deployed, the plug may seal the vessel and provide hemostasis. Such devices, however, may be difficult to position properly with respect to the vessel, which may be particularly significant since it is generally undesirable to expose the plug material, e.g., collagen, within the bloodstream, where it may float downstream and risk causing an embolism.

Another technique has been suggested that involves percutaneously suturing the puncture site, such as that disclosed in U.S. Patent No. 5,304,184, issued to Hathaway et al. Percutaneous suturing devices, however, may require significant skill by the user, and may be mechanically complex and expensive to manufacture.

U.S. Patent No. 5,478,354, issued to Tovey et al., discloses a surgical fastener including an annular base having legs that, in a relaxed state, extend in a direction substantially perpendicular to a plane defined by the base and slightly inwards toward one another. During use, the fastener is fit around the outside of a cannula, thereby deflecting the legs outward. The cannula is placed in an incision, and the fastener is slid along the cannula until the legs pierce into skin tissue. When the

cannula is withdrawn, the legs move towards one another back to the relaxed state to close the incision.

U.S. Patent Nos. 5,007,921 and 5,026,390, issued to Brown, disclose staples that may be used to close a wound or incision.

5 In one embodiment, an "S" shaped staple is disclosed that includes barbs that may be engaged into tissue on either side of the wound. In another embodiment, a ring-shaped staple is disclosed that includes barbs that project from the ring. Sides of the ring may be squeezed to separate the barbs further, and
10 the barbs may be engaged into tissue on either side of a wound. The sides may then be released, causing the barbs to return closer together, and thereby pulling the tissue closed over the wound. These staples, however, have a large cross-sectional profile and therefore may not be easy to deliver through a
15 percutaneous site to close an opening in a vessel wall.

Accordingly, devices for engaging tissue, e.g., to close a vascular puncture site, would be considered useful.

SUMMARY OF THE INVENTION

20 Applications Serial Nos. 09/732,178, filed December 7, 2000; 10/081,726, filed February 21, 2002, now Patent No. 6,623,510; 10/335,075, filed December 31, 2002; 10/081,273, filed February 21, 2002; 10/081,717, filed February 21, 2002; 10/356,214, filed

January 30, 2003 and 10/638,118, filed August 8, 2003, the disclosures of which are incorporated by reference herein, are directed to devices and methods for engaging tissue, e.g., to connect tissue segments together or to close and/or seal openings through tissue, such as in a wall of a body lumen. The present invention is directed to vascular closure devices or clips having a design particularly suitable for closing a puncture in a wall of a blood vessel formed during a diagnostic or therapeutic procedure.

10 According to the present invention, a device for engaging tissue includes a generally annular-shaped body defining a plane and disposed about a central axis extending substantially normal to the plane. The body may be movable from a substantially planar configuration lying generally in the plane towards a transverse configuration extending out of the plane. The body also includes a plurality of looped elements including alternating first and second curved regions that define an inner and outer periphery of the body, respectively, in the planar configuration. A plurality of tines or other tissue-engaging elements extend from the first curved regions, and are oriented towards the central axis in the planar configuration, and substantially parallel to the central axis in the transverse

15
20

configuration. The device may be biased towards the planar configuration, e.g., to bias the tines towards the central axis.

The looped elements of the device may generally define an endless zigzag pattern, e.g., a sinusoidal pattern, extending
5 about the central axis. The looped elements may facilitate deforming the device between the planar and transverse configurations, e.g., by distributing stresses through the device and minimizing localized stresses in the curved regions. In
10 addition, the looped elements may be expandable between expanded and compressed states for increasing and reducing a periphery of the body in the transverse orientation, respectively. The looped elements may be biased towards one of the compressed and expanded states.

Adjacent tines of the device may have a first curved region
15 disposed between them. The first curved region between adjacent tines may include a substantially blunt element extending towards the central axis. The blunt element may have a length shorter than lengths of the adjacent tines.

The tines of the device may include first and second primary
20 tines, having a first length and a second length, respectively, which may be the same as or different than one another. The first and second primary tines may be disposed on opposing first curved regions, and may be oriented substantially towards each

other in the planar configuration. In the planar configuration, the first and second primary tines may at least partially overlap the body or each other. The tines may also include one or more secondary tines having a length substantially shorter than the first and second lengths of the primary tines. The secondary tines may be disposed on either side of the first and second primary tines.

A first primary tine, having a first length, may extend from the body towards the central axis in the planar configuration, and may be deflectable out of the plane when the body is moved towards the transverse configuration. A second primary tine, having a second length, may extend from the body towards the first tine when the body is in the planar configuration, and may be deflectable out of the plane when the body is moved towards the transverse configuration. The lengths of the first and second primary tines may cause the primary tines to at least partially overlap in the planar configuration. The body may be biased towards the planar configuration to bias the tines generally towards the central axis.

The device may include a set of secondary tines having a length shorter than the first and second lengths. The secondary tines may extend from the body towards the central axis in the planar configuration, and may be deflectable out of the plane

when the body is moved towards the transverse configuration. In an exemplary embodiment, a secondary tine may be disposed on either side of the first primary tine, and a secondary tine may be disposed on either side of the second primary tine.

5 Optionally, adjacent tines may have a first curved region disposed between them. The first curved region between adjacent tines may include a substantially blunt element extending towards the central axis. The blunt element may have a length shorter than lengths of the adjacent tines.

10 Also, the device may include a plurality of looped elements disposed around a periphery of the body. The looped elements may generally define an endless zigzag pattern extending about the central axis. The first primary tine and the second primary tine may extend from looped elements disposed opposite one another.

15 The looped elements may be expandable between expanded and compressed states for increasing and reducing a periphery of the body in the transverse orientation, respectively. The looped elements may be biased towards one of the compressed and expanded states.

20 In any event, the primary tines of the clips of the present invention will be offset from the axis of symmetry of the loop from which they extend. The offsetting of the primary tines is achieved by simply relocating the primary tines which are

directly attached to the loop to a location which is not on the axis of symmetry of the loop or providing an intermediate connecting element between the tines and the axis of symmetry of the curved region of the loop from which the tine extends. This
5 connecting element is preferably straight or linear, but may also be curved. It is particularly preferred to use such a connecting element which is connected to a point or region on the axis of symmetry of the loop to enhance consistency of performance of the clip during deployment. The offsetting of the tines is believed
10 to reduce any tendency to wander during deployment, which the tines might otherwise have.

In another aspect of the present invention, a method is provided for manufacturing a clip from an elastic material, such as a sheet of superelastic alloy, e.g., a nickel-titanium alloy
15 ("Nitinol"). The components of the clip, e.g., a generally-annular body, optionally including looped elements, and/or tines, may be formed by removing portions from the sheet. The portions may be removed, e.g., by laser cutting, chemical etching, photo
chemical etching, stamping, electrical discharge machining, and
20 the like, or by the method disclosed in U.S. patent application Serial No. 10/335,075, filed December 31, 2002. The clip may be polished using one or more processes, such as electro-polishing, chemical etching, tumbling, sandblasting, sanding, and the like,

and/or heat-treated to provide a desired finish and/or desired mechanical properties. Optionally, the body and tines may be coated with a therapeutic agent, e.g., a peptide coating and/or one or more clotting factors.

5 In addition or alternatively, the clip may be disposed in a planar configuration, e.g., upon forming the clip from the sheet, and heat treated to form a clip biased to the planar configuration. For example, the clip may be formed from a shape memory material, e.g., Nitinol, that may substantially recover
10 the planar configuration when heated to a first predetermined temperature corresponding to an austenitic state, e.g., a temperature close to body temperature. The clip may be cooled to a second predetermined temperature corresponding to a martensitic state, e.g., a temperature at or below ambient temperature, and
15 malleably manipulated.

For example, the clip formed from the sheet may be deformed to a transverse configuration, such as that described above, e.g., by loading the clip onto a mandrel or directly onto a delivery device. If the clip includes looped elements formed
20 from the body, the looped elements may be biased upon heat treatment towards an expanded state, but may be malleably deformed to a compressed state upon cooling, e.g., to facilitate loading onto the delivery device. Alternatively, the clip may be

formed from a superelastic material, e.g., Nitinol, such that the clip may be resiliently deformed to the transverse configuration and/or compressed state, yet may automatically attempt to resume its planar configuration and/or expanded state upon release from
5 external forces.

The clip may also be manufactured according to the method set forth in U.S. Patent application Serial No., 10/335,075, filed December 31, 2002.

In still another aspect of the present invention, a method
10 for closing an opening in a wall of a body lumen is provided. The distal end of an elongate member may be advanced through an opening in a patient's skin, along a passage through tissue, and into the body lumen. A distal portion of an obturator may be positioned distally beyond the distal end of the elongate member
15 along the passage within the body lumen. One or more expandable elements on the distal portion of the obturator may be expanded transversely. The obturator may be withdrawn from the passage until the expandable elements contact the wall of the body lumen, thereby providing a tactile indication of a location of the wall
20 of the body lumen between the elongate member and the plurality of expandable elements of the obturator.

A clip may be advanced into the passage over the elongate member until tines of the clip penetrate the wall of the body

lumen, the tines and the expandable elements on the obturator being angularly offset from one another such that the tines penetrate the wall at locations between the expandable elements. The obturator may be collapsed, and the elongate member and/or
5 obturator may be withdrawn from the body lumen and passage, leaving the clip to substantially close the opening in the wall of the body lumen. When the elongate member is withdrawn, the tines may automatically at least partially move towards a planar configuration to substantially close the opening. The clip may
10 also be delivered to the desired site by using the apparatus and methods disclosed in U.S. patent applications Serial Nos. 10/356,214, filed January 30, 2003 and 10/638,118, filed August 8, 2003.

Advancing the clip may include puncturing the wall of the
15 body lumen with the primary tines until tips of the primary tines enter the body lumen, and puncturing the wall of the body lumen with the secondary tines. The primary tines and the secondary tines may puncture the walls without contacting the expandable elements of the obturator.

20 Other objects and features of the present invention will become apparent from consideration of the following description taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a top view of a clip including a plurality of tines in a planar orientation, in which the primary tines are offset from the axis of symmetry of the loop from which they extend and are connected to a curved region of the loop by a straight connecting element in accordance with the present invention.

Figures 1B and 1C are side views of the clip of Figure 1A, with the tines oriented substantially transversely from the planar orientation, in compressed and expanded states, respectively.

Figure 2 illustrates a clip according to the present invention in which the primary tines overlap with the body of the clip.

Figures 3A-3C illustrate top views of clips in which the primary tines are offset from the axis of symmetry of the loop from which they extend by a connecting element which is at least partially curved.

Figure 4 illustrates a clip in which the primary tines have different lengths.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Turning now to the drawings, Figures 1A-1C show a first preferred embodiment of a closure device or clip 10 for closing an incision, puncture, or other passage through tissue, e.g., communicating with a blood vessel or other body lumen (not shown). The clip 10 includes a body 12, which may be generally annular in shape and surrounds a central axis 24, a plurality of primary tines 14 and a plurality of secondary tines 16 extending from the body 12. As used herein, an "annular-shaped body" includes any hollow body, e.g., including one or more structures surrounding an opening, whether the body is substantially flat or has a significant thickness or depth. Thus, although an annular-shaped body may be circular, it may include other noncircular shapes as well, such as elliptical or other shapes that are asymmetrical about a central axis.

The body 12 includes a plurality of looped or curved elements 30 that are connected to one another to form the body 12. Each looped element 30 may include an inner or first curved region 32 and an outer or second curved region 34. In a preferred embodiment, the first and second curved regions 32, 34 are out of phase with one another and are connected alternately to one another, thereby defining an endless sinusoidal pattern. Alternatively, other generally zigzag patterns may be provided that repeat periodically, e.g., saw tooth or square tooth

patterns (not shown), instead of a sinusoidal pattern, thereby defining inner and outer regions that alternate about the body 12.

The plurality of tines 14 and 16 may be biased to extend 5 generally inwardly, e.g., towards one another and/or towards the central axis 24. The tines 14 and 16 may be disposed on the first curved regions 32, and oriented toward the central axis 24 when the clip 10 is in the planar configuration. The primary tines 14 are offset from the axis of symmetry 37 of the loops 10 from which they extend and are connected to a first curved region 32 by a straight connecting element having a longer side 35 and a shorter side 36. In a preferred embodiment, the tines 14 and 16 may be provided in pairs opposite from one another or provided otherwise symmetrically with respect to the central axis 24.

15 The tines 14 and 16 may include a variety of pointed tips, such as a bayonet tip, and/or may include barbs (not shown) for penetrating or otherwise engaging tissue. For example, to increase the penetration ability of the clip 10 and/or to lower the insertion force required to penetrate tissue, each primary 20 tine 14, as shown in Figure 1A as element 18, and each secondary tine 16 may include a tapered edge (not shown) extending towards the tip along one side of the tine 14 or 16. Alternatively, as shown in Figs. 1A-1C, each tine 14 or 16 may be provided with a

tapered edge on each side of the tine 14 or 16 extending towards the tip.

Additionally, as shown in Figures 1A-1C, the tines 14 and 16 may be disposed on alternating first curved regions 32. Thus, at least one period of a zigzag pattern may be disposed between adjacent tines 14 and 16, which may enhance flexibility of the clip 10, as explained further below.

As shown in Figures 1B and 1C (where opposite ends 33a, 33b are connected to one another), the body 12 and/or the tines 14 and 16 may be deflected such that the tines 16 extend transversely with respect to the plane defined in the planar configuration, thereby defining a transverse configuration for the clip 10. Preferably, the tines 14 and 16 are oriented substantially parallel to the central axis 24 in the transverse configuration, as shown in Figure 1B. In the transverse configuration, the body 12 may have a generally annular shape defining a length, LE_1 , that extends generally parallel to the central axis 24, and corresponds generally to an amplitude of the zigzag pattern. Preferably, the body 12 is sufficiently flexible such that the clip 10 may assume a generally circular or elliptical shape (not shown), e.g., conforming to an exterior surface of a delivery device (not shown) used to deliver the clip 10.

In a preferred embodiment, the tines 14 and 16 and/or body 12 are biased to move from the transverse configuration towards the planar configuration of Figure 1A. Thus, with the tines 14 and 16 in the transverse configuration, the tines 14 and 16 may penetrate and/or be engaged with tissue at a puncture site. When the clip 10 is released, the tines 14 and 16 may attempt to return towards one another as the clip 10 moves towards the planar configuration, thereby drawing the engaged tissue together and substantially closing and/or sealing the puncture site, as explained further below.

The looped elements 30 may distribute stresses in the clip 10 as it is deformed between the planar and transverse configurations, thereby minimizing localized stresses that may otherwise plastically deform, break, or otherwise damage the clip 10 during delivery. In addition, when the clip 10 is in the transverse configuration, the looped elements 30 may be movable between a compressed state, such as that shown in Figure 1B, and an expanded state, such as that shown in Figure 1C. Preferably, the looped elements 30 are biased towards the expanded state, but may be compressed to the compressed state, e.g., by constraining the clip 10. Alternatively, only a portion of the looped elements 30 may be biased towards the expanded state, e.g., the first curved regions 32, and/or the looped elements 30 may be

biased towards the compressed state. Furthermore, the looped elements 30 reduce the force required to be exerted on the clip 10 to transition the clip 10 from the planar configuration to the transverse configuration before loading onto a delivery device
5 (not shown).

With the clip 10 in the transverse configuration, the looped elements 30 may be circumferentially and/or radially compressed to the compressed state until the clip 10 defines a first diameter or circumference 26a, such as that shown in Figure 1B.
10 The clip 10 may be constrained in the compressed state, e.g., by loading the clip 10 onto a carrier assembly of a delivery device (not shown), as described further below. When released from the constraint, e.g., when deployed from the carrier assembly, the clip 10 may automatically expand towards the expanded state, such
15 as that shown in Figure 1C, thereby defining a second diameter or circumference 26b. Thus, the looped elements 30 may facilitate reducing the profile of the clip 10 during delivery, e.g., to facilitate introducing the clip 10 through a smaller puncture or passage. Once the clip 10 is deployed entirely from the delivery
20 device, the looped elements 30 may resiliently expand as the clip 10 returns towards the planar configuration, as explained further below.

To manufacture the clip 10 (or, similarly, any of the other clips described herein), the body 12 and the tines 14 and 16 may be integrally formed from a single sheet of material, e.g., a superelastic alloy, such as a nickel-titanium alloy ("Nitinol").

5 Portions of the sheet may be removed using conventional methods, such as laser cutting, chemical etching, photo chemical etching, stamping, using an electrical discharge machine (EDM), and the like, or the method disclosed in U.S. patent application Serial No. 10/335,075, filed December 31, 2002, to form the clip. The

10 tines 14 and 16 may be sharpened to a point, i.e., tips may be formed on the tines 14 and 16 using conventional methods, such as chemical etching, mechanical grinding, and the like.

The clip 10 may be polished to a desired finish using conventional methods, such as electro-polishing, chemical

15 etching, tumbling, sandblasting, sanding, and the like. Polishing may perform various functions depending on the method used to form the clip 10. For a clip formed by laser cutting or using an EDM, polishing may remove heat affected zones (HAZ) and/or burrs from the clip. For a clip formed by photo chemical

20 etching, polishing may create a smoother surface finish. For a clip formed by stamping, polishing may remove or reduce burrs from the bottom side of the clip, and/or may smooth the "roll"

that may result on the topside of the clip from the stamping process.

In addition or alternatively, the clip 10 may be formed from a shape memory alloy, e.g., Nitinol, with the looped elements 30 formed initially in the compressed state and/or the clip 10 in the planar configuration. With the clip 10 deformed to the transverse configuration, the clip 10 may be expanded, e.g., by applying a force radially outwards against an inner surface of the clip 10, thereby expanding the looped elements 30 to the expanded state. The looped elements 30 may then be heat treated, e.g., by heating the clip 10 to an austenitic state, to cause the looped elements 30 to "remember" the expanded state, as is known to those skilled in the art. It may also be necessary to further heat treat the clip 10 further, e.g., with the tines in the planar configuration to cause the body 12 and/or tines 14 and 16 to "remember" and be biased towards the planar configuration, as is known to those skilled in the art. The clip 10 may then be cooled, e.g., to a martensitic state, which may be at or close to ambient temperature, and manipulated, e.g., malleably deformed to the transverse configuration, for example, by loading the clip 10 onto a delivery device (not shown), as described below. Thus, if the clip 10 is subsequently heated to a predetermined temperature, e.g., at or below body temperature, the material may

remember the planar configuration and/or expanded state and become biased towards them.

Each of the primary tines 14 may have a length l_1 , although alternatively, as shown in Fig. 6, each of the primary tines 14 may have a different length than one another. The primary tines 14 may be disposed in one or more opposing pairs, e.g., on opposing first curved regions 32, and may be oriented towards and/or across the central axis 24 in the planar configuration. In the planar configuration, the lengths l_1 may be sufficiently long such that the primary tines 14 at least partially overlap one another, i.e., extend across the central axis 24 towards an opposing tine 14. Therefore, the tips of the primary tines 14 may extend past the central axis 24 and/or the primary tines 14 in each pair may lie substantially parallel to each other when the clip 10 is in the planar configuration.

Each of the secondary tines 16 may be disposed on a first or inner curved region 32, e.g., such that one or more secondary tines 16 may be provided between opposing pairs of primary tines 14. Each of the secondary tines 16 may have a length l_2 that is substantially less than the length l_1 of the primary tines 14.

Preferably, a secondary tine 16 is disposed on either side of each primary tine 14. For example, the clip 10 shown in Figures 1A-1C has first and second primary tines 14, and each of

the first and second primary tines 14 has a secondary tine 16 on either side of it. Thus, the clip 10 may have a total of two primary tines 14 and four secondary tines 16. Optionally, the secondary tines 16 may be disposed substantially symmetrically about the central axis 24. The tines 14, 16 may be provided on every other first curved regions 32. For example, a first curved region 32 having neither a primary tine 14 nor a secondary tine 16 may separate each adjacent tine, e.g., between two adjacent secondary tines 16, or between a secondary tine 16 and a primary
5
10
tine 14.

With the clip 10 in the transverse configuration, the clip 10 may be delivered such that the primary tines 14 entirely penetrate the wall of a blood vessel or other body lumen, while the secondary tines 16 only partially penetrate the wall due to their relative lengths, as explained further below.
15

As shown in Figure 1A, primary tines 14 are connected to curved regions 32 by linear regions 35 and 36 which are of different lengths. Thus, primary tines 14 are offset from the axis of symmetry 37 of the loops having the curved regions to which they are attached. The offsetting of primary tines is also
20
disclosed in parent application Serial No. 10/335,075, filed December 31, 2002, which discloses the use of curved configurations to connect the primary tines to the curved regions

of the clip. It has been found preferable to use linear, or straight, regions, as shown as elements 35 and 36 in Figure 1A to connect the primary tines 14 of the present invention to the curved regions 32.

5 Figure 2 illustrates a clip of the same general type as that of Figure 1A, but in a somewhat different embodiment in which primary tines 14a overlap body 12 at locations comprising first curved regions 32.

10 Figures 3A-3C illustrate various designs of clips configured according to the present invention in which the primary tines, which are offset from the axis of symmetry of the loop from which they extend, are connected directly to a first curved region or are connected to the curved region by extending one side of the curved region to form one side of the primary tine and connecting
15 the other side of the primary tine with a curved connecting element.

 Turning to Figures 3A-3C in more detail, Figure 3A illustrates clip 126 has body 121, primary tines 122, secondary tines 123 and loops 125. Each loop has an axis of symmetry such as that indicated by 127. The tines are provided with point 124.
20 In this embodiment, the primary tines 122 are offset from the axis of symmetry of the loop from which they extend and are connected directly to the first curved section of such loop.

In Figure 3B, the clip 136 has body 131 having primary tines 132 and secondary tines 133 is illustrated. The body 131 is provided with loops 135 and the primary tines 132 comprise a first side 137 which is an extension of a side of the loop 138
5 from which tine 137 extends and another side 139 which is connected directly to the loop from which it extends. The primary tines are offset from the axis of symmetry, indicated by 140 of the loop from which they extend.

The clip of Figure 3B is similar in some respects to the
10 clip of 3B, but is generally elliptical in shape rather than generally circular in shape. Thus, clip 237 comprises body 231 which has loops 235, primary tines 232, secondary tines 233 which tines have points 234. In this embodiment, the primary tines 232 extend beyond the innermost reach of the first curved regions
15 which are opposite the first curved regions from which the primary tines extend. The primary tines are offset from the axis of symmetry 238 of the loop from which they extend. The primary tines of the clip of Figure 3C are connected to the loops from which they extend in the same manner as those of Figure 3B.

20 Figure 4 illustrates a clip 50 in which the primary tines 51 and 52 are of different lengths. The primary tines 51 and 52 are offset from the axis of symmetry 53 of the loop from which they

extend and are connected to the loop in the same manner as the primary tines of Figure 3B.

Any of the clips of the present invention may include one or more radiopaque markers or other markers visible using external
5 imaging, such as fluoroscopy. For example, using the clip 10 of Figures 1A-1C as an example, the entire clip 10 may be coated with radiopaque material, which may be a high density material such as gold, platinum, platinum/iridium, and the like.

Alternatively, the clip 10 may be partially coated with
10 radiopaque material by using masking techniques. For example, the entire clip 10 may first be coated with radiopaque material. The clip 10 may then be masked at locations where the radiopaque coating is desired. For example, the looped elements 30 of the clip 10 may be left unmasked during this process if it is desired
15 to leave the looped elements 30 uncoated by radiopaque material. This may be desirable, e.g., to prevent radiopaque material from adversely affecting the flexibility of the looped elements 30. The clip 10 may then be treated to remove the radiopaque material from the unmasked areas, in this example, the looped elements 30.
20 The masking may then be removed using conventional processes, leaving the rest of the clip 10 coated with radiopaque material.

In another alternative, one or more discrete markers may be provided at predetermined locations on the clip 10. For example,

high density or radiopaque material may be crimped or otherwise secured onto opposing double looped or circular regions 30. In another embodiment, a plurality of pockets may be provided on the looped elements 30 into which high density plugs (not shown) may be bonded or otherwise secured. These various radiopaque markers may also be incorporated in any of the embodiments described herein.

Any of the clips of the present invention may be coated with a substance that enhances hemostasis and/or healing of a blood vessel, e.g., by increasing a rate of regeneration of endothelium on the interior surface of the vessel, or by decreasing inflammatory response at the treatment site. In one embodiment, a suitable synthetic peptide coating may be applied to a clip to attract endothelial cells to the surface. An exemplary synthetic peptide coating may, for example, attach to the same cell binding sites as collagen. In another embodiment, a clip may be coated with a combination of clotting factors in order to promote hemostasis. For example, one side of the clip may be coated with Factor III and an endopeptidase, such as PTA, to accelerate the intrinsic clotting pathway. On the opposite side of the clip, a combination of a protein cofactor proaccelerin (Factor V) and an activated endopeptidase, such as serum prothrombin conversion accelerator (SPCA), cothromboplastin, and the like, may be

applied to accelerate the extrinsic clotting pathway. The clips of the present invention may also be coated with any suitable hydrophilic polymer that swells in the presence of bodily fluids in order to reduce, minimize, or stop blood flow, thereby aiding
5 the hemostasis process.

The clips of the present invention may be delivered using various apparatus and methods. Suitable apparatus that may be used to deliver a clip of the present invention are disclosed in co-pending U.S. application Serial No. 10/081,723, filed on
10 February 21, 2002 and entitled "Apparatus and Methods for Delivering a Closure Device" and in U.S. applications Serial Nos. 10/356,214, filed January 30, 2003 and 10/638,118, filed August 8, 2003, and 10/081,725, filed February 2, 2001, which are assigned to the assignee of the present application. The
15 disclosures of these applications and any references cited therein are expressly incorporated by reference herein.

While the invention is susceptible to various modifications, and alternative forms, specific examples thereof have been shown in the drawings and are herein described in detail. It should be
20 understood, however, that the invention is not to be limited to the particular forms or methods disclosed, but to the contrary, the invention is to cover all modifications, equivalents and

alternatives falling within the spirit and scope of the appended claims.